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EXAMINER

CLOW, LORI A

ART UNIT PAPER NUMBER

1631

DATE MAILED: 06/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | | |
|------------------------------|---------------------------------|--------------------------------|--|
| Office Action Summary | Application No. 10/071,302 | Applicant(s) YANG, QINGHONG | |
| | Examiner Lori A. Clow, Ph.D. | Art Unit 1631 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 April 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-26 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-26 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicants' arguments, filed 5 April 2004, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claims 1-26 are currently pending.

The rejections of claims 1-26 under 35 USC 103(a) as being unpatentable over Yang et al, in view of Wu et al., Kumar et al., and Geisen et al. have been withdrawn in view of Applicant's showing that the invention was commonly owned at the time of invention.

The rejections of claims 1-26 under 35 USC 112, 2nd paragraph have been withdrawn in view of Applicant's amendments.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8, 12-19, and 23-25 remain rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,232,104 (Lishanski et al.).

As sated previously and re-iterated below for Applicant's convenience, Lishanski et al. teach universal method to detect any difference in two related nucleic acid sequences, whether or not such a difference is known. Differences include any mutation such as a single base mutation, deletion, or insertion that can be defined by a pair of primers for conducting the polymerase chain reaction (column 5). The invention involves formation of a four-strand cruciform DNA structure or complex. Partial duplexes are formed by amplification using three different primers in PCR and allowing products to anneal. The complex dissociates into normal duplex structures by strand exchange by means of branch migration when the double stranded portions of each partial duplex are identical. However, if there is a difference between the two double stranded portions, the complex does not dissociate and can be detected as an indication of the presence of a difference between the nucleic acids (column 5). While Lishanski et al. do not teach the

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specific mutations to the duplexes, as recited in the above claims, it would have been prima facie obvious to one of ordinary skill in the art to mutate one or the other or both of the target and reference at various places along the duplex, as motivated by Lishanski et al. at column 7 and 8: "the reference nucleic acid is a sequence that is related to the target nucleic acid in that the two are identical except for the presence of a difference, such as a mutation (column 7). A mutation may include a polymorphism (column 8)".

Applicant argues that "Lishanski et al. teaches detecting a difference between two related nucleic acids sequences (e.g., single nucleotide polymorphism) using a pair of partial duplexes that are identical except for the targeted difference[...]. Thus, Lishanski et al. does not teach the claimed method that uses a pair of partial duplexes with the target or reference having a mutation not at the targeted site of the polymorphism". This argument is not persuasive in that Lishanski et al. do teach a "method for detecting the presence of a difference between related nucleic acid sequences" (see abstract). "Two nucleic acid sequences are related when they contain at least 15 nucleotides at each end that are identical but have different lengths or have intervening sequences that differ by at least one nucleotide" (column 8, lines 6-10). Therefore, whether the mutation is at the site of polymorphism or not is irrelevant because Lishanski et al. teach the detection of any mutation. The mutation may include a polymorphism, as stated at column 8, line 24, however, a mutation is defined as a change in the sequence of nucleotides (column 8, lines 15-19), not necessarily only at the site of polymorphism.

Applicant argues that Lishanski et al. teach that "the complex [formed by two partial duplexes] dissociates into normal duplex structures by strand exchange by means of branch migration when the double stranded portions of each partial duplex are identical. However,

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where there is a difference between the two double stranded portions, the complex does not dissociate and can be detected as an indication of the presence of a difference between the nucleic acids". While this may be one embodiment of the Lishanski et al. invention, another embodiment does provide for a "complex made by the process of amplifying a target nucleic acid sequence having a mutation and a reference sequence" (column 4, lines 51-57). A mutation may be detected anywhere with the invention of Lishanski et al. Therefore, the instant invention remains anticipated.

Claims 9, 20, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,232,104 (Lishanski et al.), as applied to claims 1-8, 12-19, 23-25 above, in view of Wu et al. (Nucleic Acids Research (1998) Vol. 26, pages 5432-5440).

As stated in the previous Office Action an re-iterated below for Applicant's convenience, while Lishanski et al. teach a method of detecting the presence or absence of a difference between two related nucleic acid sequences, as described above, Lishanski et al. do not teach the specific limitation of duplexes containing GC-rich sequences, as in claims 9, 20, and 26. However, Wu et al. do teach this limitation.

Wu et al. teach that an introduction of a GC-rich sequence, through PCR using GC-clamped primers, not only prevent fragments from melting completely, but also alters the melting characteristics of the fragment (page 5432, column 2). As admitted by the specification on page 3, this technique was well known in the art at the time of the invention. It would have been obvious to one of ordinary skill in the art at the time of the invention to modify melting temperature using well-known techniques such as those taught by Wu for the duplexes of the

instant invention, as motivated by the desired stability of primers when GC-rich sequences are added.

Claims 10, 21, and 26 remain rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,232,104 (Lishanski et al.), as applied to claims 1-8, 12-19, 23-25 above, in view of Kumar et al (Nucleic Acids Research (1998) Vol. 26, pages 831-838).

As stated in the previous Office Action and re-iterated below for Applicant's convenience, Lishanski et al. do not specifically teach the specific limitation of duplexes with minor groove binding motifs, as in claims 10, 21, and 26. However, Kumar et al. do teach this limitation.

Kumar et al. show that a duplex consisting of oligodeoxyribonucleotide 5'-TGATTATCTG-3' conjugated at the 5'-end to CDPI₃ (a minor groove binding moiety) and its complementary strand to an unmodified control duplex of the same sequence using nuclear magnetic resonance had a melting temperature that was 30 degrees C higher compared to the unmodified control duplex (page 831, abstract). Thus it would have been prima facie obvious to one of skill in the art at the time of the invention to use the technique of Kumar to alter melting temperature of the duplex in the invention of Lishanski as motivated in Kumar by the desire for a more stable duplex (see abstract, page 831).

Claims 11, 22, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,232,104 (Lishanski et al.), as applied to claims 1-8, 12-19, 23-25 above, in view of Giesen et al. (Nucleic Acids Research (1998) Vol. 26, pages 5004-5006).

As stated in the previous Office Action and reiterated below for Applicant's convenience, Lishanski et al. do not teach the specific limitation of duplexes with PNAs in claims 11, 22, and 26. However, Giesen et al. do teach this limitation.

Giesen et al. teach that the two strands of a PNA/DNA hybrid lack the electrostatic repulsion as observed in DNA/DNA duplexes, giving rise to virtually ionic strength independent thermal stability (T_m). Furthermore, PNA/DNA duplexes generally have a higher melting temperature than the corresponding DNA/DNA duplexes (page 5004, column 1). Therefore, it would have been prima facie obvious at the time of the invention to use a PNA/DNA hybrid of Giesen in the instant invention to detect genotypes at the site of a mutation as motivated by the attainment of higher affinity and specificity of the PNA complexes (see abstract, page 5004).

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

No claims are allowed.

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Inquiries

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703) 308-4242, or (703) 308-4028.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lori A. Clow, Ph.D., whose telephone number is (571) 272-0715. The examiner can normally be reached on Monday-Friday from 10 am to 6:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael P. Woodward, Ph.D., can be reached on (571) 272-0722.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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June 23, 2004
Lori A. Clow, Ph.D.
Art Unit 1631
Lori A. Clow

MARJORIE MORAN
PATENT EXAMINER

Marjorie A. Moran
6/23/04